CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761164Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum

Date:	January 31, 2022
Reviewer:	Kate Gelperin, MD, MPH Division of Epidemiology I (DEPI-1)
Through:	Steven Bird, PhD, PharmD, MS, Team Leader DEPI-I
	Wei Hua, MD, PhD, MS, MHS, Associate Director DEPI-I
	Michael Blum, MD, MPH, Deputy Director Office of Pharmacovigilance and Epidemiology (OPE)
	Sarah Dutcher, PhD, Epidemiologist Team Leader (Acting) Sentinel Core Team, Regulatory Science Staff
	Robert Ball, MD, MPH, Deputy Director Office of Surveillance and Epidemiology (OSE)
Subject:	ARIA Sufficiency Memo
Drug Name(s):	Sutimlimab
Application Type/Number:	BLA 761164
Applicant/sponsor:	Bioverativ Therapeutics, Inc.
OSE RCM #:	2022-67

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Sutimlimab (BLA 761164/resubmission, ENJAYMO) is a first-in-class, humanized monoclonal antibody designed to target C1s, which is responsible for activating the classical complement pathway (CP). Sutimlimab blocks the activity of the C1s esterase, the proximal step in the activation of the CP. The proposed indication is for the treatment of hemolysis in adult patients with Cold Agglutinin Disease (CAD). The proposed dosing is 6.5g (b) (4) or 7.5g (for patients >75kg), administered as an intravenous infusion over 1-2 hours once per week for the first two doses followed by every other week dosing. FDA issued a complete response letter for sutimlimab in November 2020 because of deficiencies related to commercial manufacturing and data integrity that were observed at the FDA pre-license inspection of the (b) (4). drug substance manufacturing facility.[1] The Application was resubmitted by Bioverativ USA Inc. (A Sanofi Company) on August 5, 2021.[2]

Cold agglutinin disease (CAD) is a form of autoimmune hemolytic anemia in which cold agglutinins can cause clinical symptoms related to agglutination of red blood cells (RBCs) and hemolytic anemia. Cold agglutinins are autoantibodies that recognize antigens on RBCs at temperatures below normal core body temperature. Hemolysis in CAD is primarily extravascular and mediated by complement. Primary CAD is a rare disease, with prevalence of 16 per million inhabitants in a population-based retrospective study from Norway.[3] The mean age at presentation of CAD is in the mid to late 60s. Severity can range from compensated hemolysis without anemia to severe hemolytic anemia requiring transfusion. Treatment is directed at minimizing cold-induced symptoms, maintaining an acceptable hemoglobin level, and, if required, addressing underlying disorders. Compensated hemolysis may not require specific treatment. The association of CAD with B-cell or plasma cell lymphoproliferative disorders has been described.[4] Off-label use of immunosuppressive therapies, alone or in combination with cytotoxic therapies (e.g., rituximab with or without fludarabine or bendamustine) is a therapeutic option, but time to response can be months.[5]

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[1] FDA Joint Supervisory Review for Regulatory Action; Sutimlimab (BLA 761164, ENJAYMO); Complete Response; dated November 11, 2020; DARRTS Reference ID: 4701396

[2] CDER OPQ Review BLA 761164; Number 2; Date January 6, 2022; DARRTS Reference ID: 4916246

[3] Berentsen S, Ulvestad E, Langholm R, et al. Primary chronic cold agglutinin disease: a population based clinical study of 86 patients. Haematologica. 2006 Apr;91(4):460-6. PMID: 16585012

[4] Brugnara C, Berentsen S, Mentzer WC, Tirnauer JS (2021). Cold agglutinin disease. In T.W. Post, P. Rutgeerts, & S. Grover (Eds.), *UptoDate*. Available from https://www.uptodate.com/contents/cold-agglutinin-disease?source=history_widget

[5] Berentsen S. How I treat cold agglutinin disease. Blood. 2021 Mar 11;137(10):1295-1303. doi:

1.2. Describe the Safety Concern

The efficacy of sutimlimab in patients with cold agglutinin disease (CAD) was assessed in an open-label, single-arm, 6-month study in 24 patients (CARDINAL Trial, NCT03347396). Following the completion of the 6-month treatment period, patients continued to receive sutimlimab in a long-term safety and durability of response extension phase for an additional 24 months. Among patients receiving sutimlimab, 92% completed 26 weeks of therapy; the median duration of treatment was 26.1 weeks. The long-term safety of sutimlimab in patients with cold agglutinin disease (CAD) has not been characterized. Unlike C5 complement inhibitors, sutimlimab leaves the alternative pathway intact. However, patients may still be at risk for serious infections due to the inhibition of C1s. In clinical studies, no patient has been reported to develop a meningococcal infection; however, all participants were vaccinated against encapsulated bacteria (*Neisseria meningitidis, Haemophilus influenzae,* and *Streptococcus pneumoniae*) prior to receiving sutimlimab. One patient in the 90-day safety follow-up report from study BIVV009-03 Part B developed Streptococcus pneumoniae bacteremia, despite receiving a vaccination. There is also a potential risk that inhibition of the C1s may predispose patients to the development of autoimmune diseases. In the clinical development program of sutimlimab, some patients who previously had a negative autoantibody before exposure, had one or more positive tests in the autoantibody panel following exposure to sutimlimab. While no patient had a new diagnosis of an autoimmune disease, there was one patient with a history of polymyalgia rheumatica who discontinued the study due to arthralgias with a positive anti-nuclear antibody (ANA) test.[6,7]

FDA/CDER Division of Nonmalignant Hematology (DNH) would like a post-market study to further characterize the long-term safety of sutimlimab with at least 5 years of follow-up. Outcomes of interest include major safety findings from the registry, including the occurrence of autoimmune diseases such as systemic lupus erythematosus (SLE), as well as serious infections. All patients in the registry should be followed for the occurrence of autoantibody development and development or worsening of autoimmune diseases to include but not limited to systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody vasculitis, antiphospholipid syndrome, membranous nephropathy, myasthenia gravis, neuromyelitis optica, or any SLE-like diseases and mesangial proliferative glomerulonephritis.

10.1182/blood.2019003809. PMID: 33512410.

[6] Maureen DeMar RPM, OCHEN / DNH; Request for Consultation, Sutimlimab (BLA 761164, ENJAYMO) dated January 6, 2022; DARRTS Reference ID: 4915863

[7] Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, Kuter DJ, Jilma B, Tvedt THA, Fruebis J, Jiang X, Lin S, Reuter C, Morales-Arias J, Hobbs W, Berentsen S. Sutimlimab in Cold Agglutinin Disease. N Engl J Med. 2021 Apr 8;384(14):1323-1334. doi: 10.1056/NEJMoa2027760. PMID: 33826820

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

	Serious Infections	Autoimmune Diseases
Assess a known serious risk		
Assess signals of serious risk	X	X
Identify unexpected serious risk when available data indicate potential for serious risk		

1.4. Statement of Purpose

The purpose of the postmarket study is to provide a descriptive characterization of the long term (5-year) safety profile of sutimlimab, with a focus on: 1) the risk of serious infections, especially those caused by encapsulated bacteria, and 2) the development of new or worsening autoimmune diseases.

1.5. Effect Size of Interest or Estimated Sample Size Desired

This is an observational prospective descriptive study aiming to characterize long-term clinical safety of sutimlimab therapy for patients with CAD, a rare disease. No target sample size has been specified.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired population consists of patients diagnosed with cold agglutinin disease (CAD).

2.2 Is ARIA sufficient to assess the intended population?

Yes. Because CAD will be the only indication for sutimlimab after initial approval, the exposure should be adequate to identify the intended population.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is sutimlimab.

3.2 Comparator Exposure(s)

Not applicable.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. Sutimlimab is expected to be identifiable through injection procedure codes post approval.

4 OUTCOME(S)

4.1 Outcomes of Interest

1) Autoimmune diseases, including but not limited to systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody vasculitis, antiphospholipid syndrome, membranous nephropathy, myasthenia gravis, neuromyelitis optica, or any SLE-like diseases and mesangial proliferative glomerulonephritis
2) Serious infections overall and those caused by encapsulated bacteria

4.2 Is ARIA sufficient to assess the outcomes of interest?

No. ARIA is not sufficient to assess the outcomes of interest for the following reasons:

Diagnostic codes are available for many autoimmune diseases. Diagnosis and treatment coding could be combined to identify many of them. However, since comprehensive ascertainment of autoimmune conditions of interest will be necessary to achieve the goals of this study, it is unlikely that ARIA would have sufficient sensitivity for identification of this outcome, or the availability of detailed clinical information required to characterize diverse and complex autoimmune diseases (e.g., clinical laboratory results confirming diagnosis). The large number of autoimmune diseases makes this a highly challenging outcome. Thus, ARIA is insufficient for autoimmune diseases.

Although ARIA has algorithms to identify serious infections, available algorithms are not currently able to characterize infections as specifically due to encapsulated bacteria. Because identification of encapsulated bacterial infections is critical to this study, ARIA is not sufficient for this outcome.

A goal of the postmarket study is to monitor patients for five years after sutimlimab initiation for occurrence of these outcomes, making post-index observation time a limitation of ARIA.

5 COVARIATES

5.1 Covariates of Interest

Detailed data on immunization status is important for all patients receiving sutimlimab, with particular emphasis on meningococcal and pneumococcal vaccines. Additionally, it is important to know if patients receiving sutimlimab are not fully vaccinated against encapsulated bacteria. Proposed labeling includes a recommendation to “vaccinate patients against encapsulated bacteria at least two weeks prior to initiation” of sutimlimab therapy due to the increased risk of serious infection with encapsulated bacteria, and to “revaccinate patients in accordance with ACIP recommendations.”

5.2 Is ARIA sufficient to assess the covariates of interest?

No, ARIA is not sufficient. Vaccination history is a key component for understanding the

utility of mitigation measures for serious infections, and this cannot be adequately obtained with a limited lookback period available in claims data.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The intended study design is an observational patient registry with descriptive data analysis to evaluate the long-term (five year) safety of sutimlimab.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA is sufficient for the design/analytic tools.

7 NEXT STEPS

Secondary data are inadequate, and primary data collection will be needed to address the safety concerns. FDA requires the Applicant to conduct PMR study 4216-1, as follows:

Conduct a registry study to characterize the long-term safety (up to 5 years) of sutimlimab in patients with primary Cold Agglutinin Disease. Yearly interim reports and the final study report should include a summary of the major safety findings for all patients in the registry including: the development or worsening of autoimmune diseases, all serious bacterial infections including encapsulated organisms, and detailed clinical information regarding events of interest such as sutimlimab dosing, meningococcal and pneumococcal vaccination status, serotype/serogroup information on any Streptococcus pneumoniae and Neisseria meningitidis isolates obtained from patients in the registry when available, concomitant medications, treatment and outcome of event.

The Applicant has agreed to conduct this study according to the following schedule:

Draft Protocol Submission: 09/2022
Final Protocol Submission: 04/2023
Annual Interim Report #1: 08/2024
Annual Interim Report #2: 08/2025
Annual Interim Report #3: 08/2026
Annual Interim Report #4: 08/2027
Annual Interim Report #5: 08/2028
Annual Interim Report #6: 08/2029
Annual Interim Report #7: 08/2030
Final Report Submission: 10/2031

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/21/2021

To: Maureen DeMar, BSN, RN, Regulatory Project Manager,
Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENJAYMO (sutimlimab-jome) injection, for intravenous use

BLA: 761164

In response to DNH consult request dated August 26, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for ENJAYMO (sutimlimab-jome) injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Maureen DeMar) on December 9, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on 12/10/21 and on 11/16/21, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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JENNIFER W CHEN
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 21, 2021
To:	Maureen DeMar, BSN, RN Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ENJAYMO (sutimlimab-jome)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761164
Applicant:	Bioverativ Therapeutics, Inc.

1 INTRODUCTION

On August 5, 2021, Bioverativ Therapeutics, Inc. submitted for the Agency's review a class 2 resubmission of their original Biologics License Application (BLA) 761164 for ENJAYMO (sutimlimab-jome) injection in response to a Complete Response (CR) letter issued on November 13, 2020. The proposed indication for ENJAYMO (sutimlimab-jome) injection is for treatment of hemolysis in adult patients with cold agglutinin disease (CAD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on August 26, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ENJAYMO (sutimlimab-jome) injection.

2 MATERIAL REVIEWED

- Draft ENJAYMO (sutimlimab-jome) injection MG received on August 5, 2021, and received by DMPP and OPDP on December 9, 2021.
- Draft ENJAYMO (sutimlimab-jome) injection Prescribing Information (PI) received on August 5, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 9, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 14, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761164
Product Name and Strength:	Enjaymo (sutimlimab-jome) injection, 1,100 mg/22 mL (50 mg/mL)
Applicant/Sponsor Name:	Bioverativ USA Inc.
OSE RCM #:	2020-515-4
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on December 10, 2021 for Enjaymo. We reviewed the revised container label to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and memorandum[b].

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Karpow, C. Label and Labeling Review for Enjaymo (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 03. RCM No.: 2020-515-2.

[b] Karpow, C. Label and Labeling Memorandum for Enjaymo (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 22. RCM No.: 2020-515-3.

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/s/

CELESTE A KARPOW
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 22, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761164
Product Name and Strength:	Enjaymo (sutimlimab-jome) injection, 1,100 mg/22 mL (50 mg/mL)
Applicant/Sponsor Name:	Bioverativ USA Inc.
OSE RCM #:	2020-515-3
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 16, 2021 for Enjaymo. We reviewed the revised container label and carton labeling to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented our recommendation on the carton labeling and we have no additional recommendations for the carton labeling at this time.

However, the container label is unacceptable from a medication error perspective because the Medication Guide statement appears on the principal display panel (PDP).

[a] Karpow, C. Label and Labeling Review for Enjaymo (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 03. RCM No.: 2020-515-2.

3 RECOMMENDATIONS FOR BIOVERATIV USA INC.

We recommend the following be implemented prior to approval of this BLA:

A. Container label

   a. The statement, “Attention Pharmacist: Each patient is required to receive the enclosed Medication Guide.” appears on the principal display panel (PDP). We are concerned that the addition of this statement clutters the container label and detracts from other important information. We recommend you delete this statement form the container label as it is not needed on the container label. In addition, we recommend moving the statement “Single-dose vial. Discard unused portion.” to the PDP.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 3, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761164
Product Name, Dosage Form, and Strength:	Enjaymo (sutimlimab-jome) injection, 1,100 mg/22 mL (50 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bioverativ USA Inc.
FDA Received Date:	August 5, 2021
OSE RCM #:	2020-515-2
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Bioverativ USA Inc. submitted a response to complete response for BLA 761164 Enjaymo (sutimlimab-jome) injection on August 5, 2021. Enjaymo is a classical complement pathway inhibitor proposed for the treatment of hemolysis in adult patients with cold agglutinin disease (CAD). We evaluated the proposed container label, carton labeling, Prescribing Information (PI), and Medication Guide (MG) for areas of vulnerability that could lead to medication errors.

REGULATORY HISTORY

BLA 761164 Enjaymo (sutimlimab-jome) injection was originally submitted as part of a rolling submission completed on March 13, 2020. The application received a complete response on November 13, 2020 due to facility inspection issues. DMEPA completed a label and labeling review[a] and memo[b] and our recommendations were conveyed to the Applicant.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] DeGraw, S. Label and Labeling Review for Enjaymo (sutimlimab-jome) (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 29. RCM No.: 2020-515.

[b] DeGraw, S. Label and Labeling Review for Enjaymo (sutimlimab-jome) (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 22. RCM No.: 2020-515-1.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, PI, and MG for Enjaymo (sutimlimab-jome) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the MG, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented. We find the PI acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed MG, container label, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Bioverativ in Section 4.2 below.

RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Medication Guide (MG)

1. How Supplied/Storage and Handling Section

    a. We note the abbreviation, “I.V.” appears in the ‘How should I receive ENJAYMO?” section of the MG. Consider removing the abbreviation, “I.V.” to prevent misinterpretation and confusion.

RECOMMENDATIONS FOR BIOVERATIV USA INC.

We recommend the following be implemented prior to approval of this BLA:

A. Container Label and Carton Labeling

1. We note the usage of the symbol “-“ in the storage statement, “Store refrigerated at 36°F-46°F (2°C-8°C) in the original carton to protect from light.” We recommend removing the use of the symbol and replacing it with the intended meaning, “to”. Revise to “**Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze. Do not shake.**” for consistency with the prescribing information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Enjaymo received on August 5, 2021 from Bioverativ USA Inc..

Table 2. Relevant Product Information for Enjaymo	
Initial Approval Date	N/A
Nonproprietary Name	sutimlimab-jome
Indication	treatment of hemolysis in adult patients with cold agglutinin disease (CAD)
Route of Administration	Intravenous (infusion)
Dosage Form	injection
Strength	1,100 mg/22 mL (50 mg/mL)
Dose and Frequency	The recommended dosage of ENJAYMO for patients with CAD is based on body weight. For patients weighing 39 kg to less than 75 kg, the recommended dose is 6,500 mg and for patients weighing 75 kg or more, the recommended dose is 7,500 mg. Administer ENJAYMO intravenously weekly for the first two weeks, with administration every two weeks thereafter.
How Supplied	one 1,100 mg/22 mL (50 mg/mL) single-dose vial per carton
Storage	Refrigerate at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze.
Container Closure	(b) (4) vial, a 20mm (b) (4) stopper, and a 20mm aluminum seal with (b) (4) cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 18, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, "sutimlimab". Our search identified 2 previous reviews[c,d], and we considered our previous recommendations to see if they are applicable for this current review.

[c] DeGraw, S. Label and Labeling Review for Enjaymo (sutimlimab-jome) (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 29. RCM No.: 2020-515.

[d] DeGraw, S. Label and Labeling Review for Enjaymo (sutimlimab-jome) (BLA 761164). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 22. RCM No.: 2020-515-1.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Enjaymo labels and labeling submitted by Bioverativ USA Inc..

- Container label received on August 5, 2021
- Carton labeling received on August 5, 2021
- Prescribing Information (Image not shown) received on August 5, 2021, available from \\CDSESUB1\evsprod\bla761164\0043\m1\us\annotatedpi.doc

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 22, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761164
Product Name and Strength:	Enjaymo (sutimlimab-jome) injection 1,100 mg/22 mL (50 mg/mL)
Applicant/Sponsor Name:	Bioverativ USA Inc., a Sanofi Company (Bioverativ)
FDA Received Date:	October 1, 2020
OSE RCM #:	2020-515-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Bioverativ submitted a revised container label and carton labeling for Enjaymo (sutimlimab-jome) on October 1, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We reviewed the revised label and labeling to determine if they are acceptable from a medication error perspective.

2 DISCUSSION AND CONCLUSION

We note that our previous recommendations were implemented. We conclude the revised container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] DeGraw, S. Label and Labeling Review for Enjaymo (sutimlimab-jome) BLA 761164. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 29. RCM No.: 2020-515.

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Division of Nonmalignant Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	**ENJAYMO (sutimlimab-jome) injection, for intravenous use**
Applicant	Bioverativ Therapeutics
Application/Supplement Number	BLA 761164
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	Treatment of hemolysis in adult patients with cold agglutinin disease (CAD)
Date FDA Received Application	03/13/2020
Review Classification (Priority/Standard)	Priority
Action Goal Date	11/13/2020
Review Date	09/29/2020
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: This application is for a NME, sutimlimab (proposed trade name: Enjaymo) for the treatment of hemolysis in adult patients with cold agglutinin disease.

Reviewer Comments: There were three interdisciplinary labeling meetings held to review and edit the labeling. I reviewed and edited the labeling before the labeling meetings were conducted. The attached version was after one round with the Applicant and is the version sent to the Applicant on 9/18/20. The labeling is due back from the Applicant on 9/30/20.

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

Regulatory Recommendation: This NDA is recommended for approval from the labeling perspecitve upon completion of labeling negotiations.

Attachments: Revised labeling with track changes edits and bubble comments explaining the revisions.

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VIRGINIA E KWITKOWSKI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 7, 2020
To:	Maureen DeMar, BSN, RN Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ENJAYMO (sutimlimab-jome)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761164
Applicant:	Bioverativ Therapeutics, Inc.

1 INTRODUCTION

On March 13, 2020, Bioverativ Therapeutics, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761164 for ENJAYMO (sutimlimab-jome) injection. The proposed indication for ENJAYMO (sutimlimab-jome) injection is the treatment of hemolysis in adult patients with cold agglutinin disease (CAD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on April 6, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ENJAYMO (sutimlimab-jome) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft ENJAYMO (sutimlimab-jome) MG received on March 13, 2020, and received by DMPP and OPDP on July 28, 2020.
- Draft ENJAYMO (sutimlimab-jome) Prescribing Information (PI) received on March 13, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 28, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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EMILY M DVORSKY
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SHAWNA L HUTCHINS
08/07/2020 09:04:30 AM

LASHAWN M GRIFFITHS
08/07/2020 09:06:19 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 3, 2020

To: Maureen DeMar, BSN, RN, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Enjaymo (sutimlimab-xxxx) injection, for intravenous use

BLA: 761164

In response to DNH's consult request dated April 6, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for Enjaymo.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Charlene Wheeler) on July 27, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 13, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 29, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761164
Product Name, Dosage Form, and Strength:	Enjaymo (sutimlimab-jome) injection 1,100 mg/22 mL (50 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bioverativ USA Inc., a Sanofi Company (Bioverativ)
FDA Received Date:	March 13, 2020
OSE RCM #:	2020-515
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Bioverativ USA Inc. submitted BLA 761164 Enjaymo (sutimlimab-jome) injection on March 13, 2020 as part 3 of 3 of a rolling submission. Enjaymo is a classical complement pathway inhibitor proposed for the treatment of hemolysis in adult patients with cold agglutinin disease (CAD). We evaluated the proposed container label, carton labeling, Prescribing Information (PI), and Medication Guide (MG) for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, PI, and MG for Enjaymo (sutimlimab-jome) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented. We find the MG acceptable from a medication error perspective.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Bioverativ in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. General Comments
    1. Replace "sutimlimab-xxxx" with the conditionally acceptable nonproprietary name "sutimlimab-jome" wherever it appears.
    2. Throughout the PI, numbers greater than or equal to 1,000 are expressed without a comma (i.e., 1100, 6500, 7500). We recommend stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".[a]

B. Highlights of Prescribing Information
    1. Dosage and Administration
        a. The dosage table presents doses in grams which is inconsistent with the product strength and the doses presented in Table 2 which are expressed in milligrams. We recommend using a consistent unit of measure throughout the PI that aligns with the unit of measure on the container label and carton labeling (i.e., milligrams). Additionally, we recommend including a unit of measure after each numerical dose to improve readability and clarity.
        b. The expression of the body weight range in column 1 should be revised to improve clarity by removing the (b) (4) statement.
        c. The dosage table contains a citation for a footnote, but the footnote is not defined. We recommend removing the citation or adding the footnote.
        d. We recommend specifying whether the body weight range is actual body weight or ideal body weight.

(b) (4)

C. Dosage and Administration [2]
    1. Recommended Dosage Regimen [2.2]
        a. We recommend revising the dosage statements to read (b) (4) as all dosage information is contained within the table.
        b. We recommend revising (b) (4) as noted above.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

2. Preparation and Administration [2.3]
    a. As the appropriate administration method is already stated (i.e., intravenous infusion only), we recommend deleting (b) (4)
    b. We recommend revising the second sentence and separating it into two lines to improve clarity and readability. Revise to read:

        Each vial of ENJAYMO is intended for single-dose only.

        Use aseptic technique to prepare Enjaymo as follows:

    c. We recommend removing the statement (b) (4) from the first bullet point as this action is implied.
    d. To improve readability, we recommend revising *Table* (b) (4) *Infusion Reference Table* to remove the (b) (4) statements in the body weight range column, specify actual or ideal body weight, and to add a unit of measure after each number in the dose column.

D. How Supplied/Storage and Handling [16]
    1. As currently presented, the NDC is represented by a placeholder. We recommend requesting the proposed NDC for review.

4.2 Recommendations for Bioverativ USA Inc

A. General Comments for all Labels and Labeling
    1. Replace "sutimlimab-xxxx" with the conditionally acceptable nonproprietary name "sutimlimab-jome" wherever it appears.

    2. We note that the strength "1100 mg" is presented without a comma. We recommend stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting "1100" as "110" or "11000".[b]

    3. We note the use of a placeholder for the NDC (i.e., 00000-000-00). We request you submit your proposed NDC for review.

B. Container (Vial) Label
    1. We recommend adding the statement "Discard unused portion" after the "Single-dose vial" statement.

    2. As currently presented, it is unclear if the linear barcode can be used by healthcare professionals for product identification. The drug barcode is often

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Please confirm the linear barcode contains the NDC number.

C. Carton Labeling

1. We note the inclusion of a medication guide as part of the labeling submission. Therefore, please add (b) (4) prominently, as space will allow, on the principal display panel per 21 CFR 208.24(d).

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Enjaymo received on March 13, 2020 from Bioverativ USA Inc..

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Enjaymo</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>sutimlimab-jome</td></tr>
<tr><td>Indication</td><td>treatment of hemolysis in adult patients with cold agglutinin disease (CAD)</td></tr>
<tr><td>Route of Administration</td><td>Intravenous (infusion)</td></tr>
<tr><td>Dosage Form</td><td>Injection (solution)</td></tr>
<tr><td>Strength</td><td>1,100 mg/22 mL (50 mg/mL)</td></tr>
<tr><td>Dose and Frequency</td><td>6,500 mg or 7,500 mg (based on weight) administered as an intravenous infusion on Day 0, Day7, and every other week starting on Day 21.
<table>
<tr><th>Body Weight Range</th><th>Initial Dose (Day 0)</th><th>Second Dose (Day 7)</th><th>Maintenance Dose (every other week, beginning on Day 21)</th></tr>
<tr><td>39 kg to less than 75 kg[1]</td><td>6,500 mg</td><td>6,500 mg</td><td>6,500 mg</td></tr>
<tr><td>75 kg or more</td><td>7,500 mg</td><td>7,500 mg</td><td>7,500 mg</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Clear to slightly opalescent, colorless to slightly yellow, preservative-free solution supplied as one 1,100 mg/22 mL (50 mg/mL) single-dose vial per carton.</td></tr>
<tr><td>Storage</td><td>Store vials refrigerated at 2°C-8°C (36°F-46°F) in the original carton to protect from light. Do not freeze. Do not shake. Discard unused portion.</td></tr>
</table>

APPENDIX F. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,[c] along with post-market medication error data, we reviewed the following Enjaymo labels and labeling submitted by Bioverativ USA Inc. on March 13, 2020:

- Container Label
- Carton Labeling
- Prescribing Information (no image shown)
  \\cdsesub1\evsprod\bla761164\0003\m1\us\proposedpi.doc
- Medication Guide (no image shown)
  \\cdsesub1\evsprod\bla761164\0003\m1\us\proposedmg.docx

G.2 Labels and Labeling

Container Label – Vial Label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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CLINICAL INSPECTION SUMMARY

Date	July 13, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Carrie Diamond, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Director Latrice Wilson, Regulatory Project Manager Division of Nonmalignant Hematology (DNH /OCHEN)
BLA	761164
Applicant	Bioverativ USA, Inc
Drug	Enjaymo™ (sutimlimab)
NME	Yes
Division Classification	Humanized monoclonal antibody directed against the classical pathway complement factor C1s
Proposed Indication	Treatment of adult patients with hemolysis in cold agglutin disease (CAD)
Consultation Request Date	May 4, 2020 (**BREAKTHROUGH**/Priority Review)
Summary Goal Date	July 31, 2020
Action Goal Date	September 1, 2020
PDUFA Date	September 13, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from a single-arm trial, Study BIVV009-03, was submitted to the Agency in support of a Biologic License Application (BLA 761164) for sutimlimab for treatment of hemolysis in adult patients with cold agglutinin disease (CAD).

A single clinical investigator (Dr. David Kuter) and the sponsor (Bioverativ) were inspected for Study BIVV009-03, an open-label, single-arm, six-month study in 24 patients, in support of BLA 761164.

Based on the results of inspections, the study data derived from Dr. David Kuter and Bioverativ are considered reliable, and the study in support of this application appears to have been conducted adequately.

II. BACKGROUND

Cold agglutinin disease (CAD) causes predominantly extravascular hemolysis and anemia via complement activation. Sutimlimab is a humanized monoclonal antibody directed against the classical pathway complement factor C1s.

The sponsor proposes this new molecular entity for the indication of the treatment of adult patients with hemolysis in cold agglutin disease (CAD). A single study, Study BIVV009-03, forms the basis for the regulatory decision-making process for this application.

Study BIVV009-03

Study BIVV009-03 was an open-label, single-arm, two-part Phase 3 study designed to evaluate the efficacy, safety, and tolerability of sutimlimab in patients with the complement-mediated disorder, cold agglutinin disease, with a recent history of blood transfusion.

The primary objective of Part A was to determine whether sutimlimab administration resulted in at least 2 g/dL increase in hemoglobin levels or increases hemoglobin to at least 12 g/dL and obviated the need for blood transfusion during treatment in patients with cold agglutinin disease, who had a recent history of blood transfusion. Part B is ongoing and will evaluate the long-term safety.

Confirmed diagnosis of primary cold agglutinin disease was based on the following criteria: chronic hemolysis, poly-specific direct antiglobulin test positive, monospecific direct antiglobulin test strongly positive for C3d, cold agglutinin titer at least 64 at 4°C, IgG direct antiglobulin test one or less than one positive, no overt malignant disease, and history of at least one documented blood transfusion within six months of enrollment and hemoglobin level 10.0 g/dL or less. The duration of treatment was 25 weeks. The duration of study observation was 26 weeks.

The primary study efficacy endpoint was treatment response rate. A patient was considered a responder to treatment if the patient did not receive a blood transfusion from Week 5 through Week 26 (end of treatment), and if the patient did not receive treatment for cold agglutinin disease, including concomitant medications, beyond what was permitted per protocol. Additionally, the patient's Hemoglobin level met either of the following criteria:

- Hemoglobin level was ≥12 g/dL at the treatment assessment endpoint (defined as the mean value from Weeks 23, 25, and 26) or
- Hemoglobin level increased by ≥2 g/dL from baseline (defined as the last hemoglobin value before administration of the first dose of study drug) at the treatment assessment endpoint.

The secondary efficacy endpoints included mean change in bilirubin, mean change in quality of life measures, mean change in LDH, number of transfusion and units after Week 5, and mean change in hemoglobin.

Study BIVV009-03 was conducted at 16 clinical investigational study sites that enrolled at least a single patient in the United States, Australia, Germany, France, Italy, Japan, Norway, and the United Kingdom.

The first patient enrolled on March 5, 2018. For Part A of the study, the last patient completed on July 11, 2019. There were 24 enrolled study subjects in this study, and every enrolled patient received treatment. Part B of the study is ongoing long-term safety, tolerability and durability of treatment effect of sutimlimab clinical investigation.

III. RESULTS (by site)

1. **David Kuter, M.D., D.Phil.., Site # 931**
   Massachusetts General Hospital
   55 Fruit St.
   Boston, MA 02114
   Inspection dates: May 20 to 21, 2020

   The institutional review board for this study was (b) (4)

   (b) (4) the MGH site under Study BIVV009-03. (b) (4)

   Source documents were reviewed (b) (4) medical records, correspondence between the clinical investigator and the sponsor, correspondence between the principal investigator and the Institutional Review Board, the sponsor monitoring log, all informed consent forms and revisions, adverse event records, and accountability for the study drug. Source documents were verified against the case report forms and sponsor data line listings.

   The primary efficacy endpoint was verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

   (b) (4) In general, this clinical investigator appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. **Bioverativ USA, Inc.**
   55 Corporate Drive
   Bridgewater, NJ 08807

   Inspection dates: June 17 to 23, 2020

   This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study BIVV009-03 (24 enrolled study patients).

   The inspection included review of organizational charts, vendor oversight, contracts and transfer of obligations, investigator agreements, financial disclosures, monitoring plans,

monitoring reports, monitor qualifications, adverse events evaluation and reporting, protocol deviations, standard operating procedures, monitoring logs, Form FDA-1572, Statement Investigator, delegation of authority log, drug accountability, record retention, and the evaluation of the adequacy of monitoring and corrective actions taken by the firm.

Sponsor performed routine audits and followed up on the audits. The study monitoring plan appeared to be adequate. Study site monitoring files were reviewed for these four clinical sites: #931, #100, and #181, and #920. All corrective and preventive action plans were resolved in a timely manner. Sponsor's monitoring of all investigator sites appeared to be adequate. There was no evidence of adverse event underreporting to the FDA.

A Form FDA 483 was not issued at the end of the study inspection. In general, the sponsor appeared to be in compliance with Good Clinical Practice. Bioverativ maintained adequate oversight of clinical trials.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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07/13/2020 02:08:44 PM